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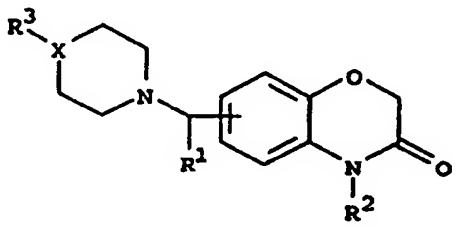
(54) Title: BENZOXAZINONE DOPAMINE D4 RECEPTOR ANTAGONISTS

(57) Abstract

Compounds having formulae (I) or (II) wherein R^1 and R^2 are independently hydrogen or C_1-C_6 alkyl; X is N or CH; and R^3 is phenyl, naphthyl, heteroaryl, substituted phenyl, substituted naphthyl or substituted heteroaryl, wherein each substituent is independently selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, -CN, $-CF_3$, or sulphonamido, and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof, are antagonists of dopamine D4 receptors.



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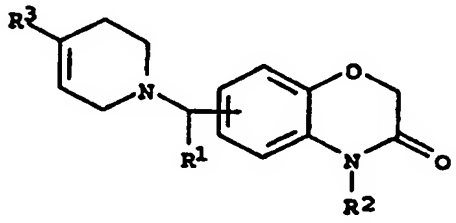

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BENZOXAZINONE DOPAMINE D4 RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

This invention relates to compounds that are antagonists at dopamine D4 receptors, to methods of treating psychosis and schizophrenia using a compound that is an antagonist at dopamine D4 receptors, and to pharmaceutically acceptable compositions that contain a dopamine D4 receptor antagonist.

BACKGROUND OF THE INVENTION

Dopamine is a neurotransmitter that is found in the brains of animals, including humans, and is essential for proper nerve signal transmission. It is well-known that certain compounds block or inhibit the binding of dopamine to dopamine receptors. Such compounds are called dopamine receptor antagonists. It is also well-known that dopamine receptor antagonists are useful in the treatment of schizophrenia and psychosis.

Recently, it has been discovered that more than one type of dopamine receptor exists, and that dopamine receptor antagonists can preferentially inhibit one type of dopamine receptor over another. Two major families of dopamine receptors have been identified and named the D1 and D2 families. In the D2 family, three distinct receptor subtypes have been identified as D2, D3, and D4.

The distribution and concentration of the subtypes of receptors varies in different regions of the brain. D2 subtype receptors are located in both the limbic region of the brain, which is associated with cognition and emotional function, and in the striatum, which is

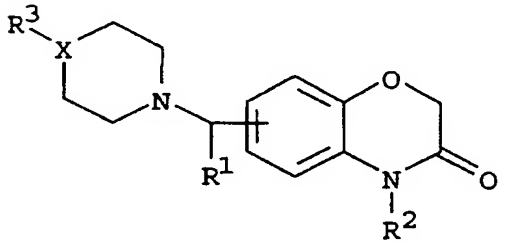
associated with motor effects. D4 receptors are found in higher concentrations in the frontal cortex and limbic regions, which are associated with cognitive and emotional function.

Antipsychotic drugs that are D2 subtype receptor antagonists have been used to treat psychosis and schizophrenia, but have undesirable extrapyramidal side effects and produce tardive dyskinesia. In contrast, D4 receptor antagonists show a lack of extrapyramidal side effects and tardive dyskinesia. Moreover, it has been observed that the levels of dopamine D4 receptors are elevated in schizophrenics.

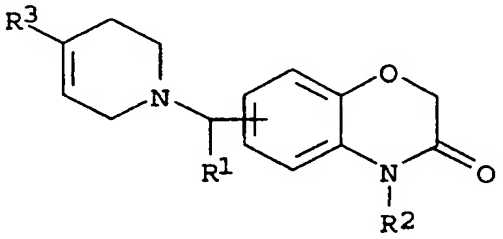
Thus, it would be useful to have compounds that are selective D4 antagonists for the treatment of psychosis and schizophrenia.

SUMMARY OF THE INVENTION

The present invention provides compounds of the Formulas I and II



I



II

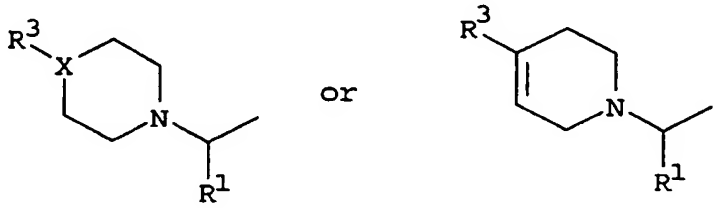
wherein R^1 and R^2 are independently hydrogen or C_1-C_6 alkyl;

X is N or CH; and

R^3 is phenyl, naphthyl,heteroaryl, substituted phenyl, substituted naphthyl or substituted heteroaryl,

wherein each substituent is independently selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, -CN, -CF_3, or sulphonamido, and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

In a preferred embodiment of Formula I or II, the group



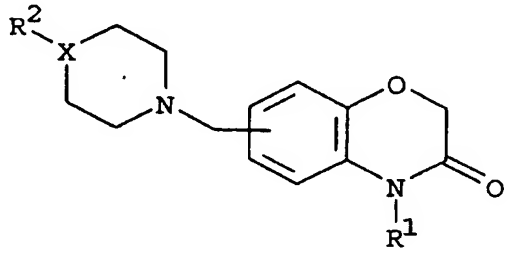
is attached to the benzoxazinone group at the 6 or 7 position.

In another preferred embodiment, R^1 and R^2 are hydrogen.

In another preferred embodiment, R^3 is phenyl, methyltolyl, tolyl, or sulfonamido.

In another preferred embodiment, X is N.

The present invention also provides compounds of Formula III,

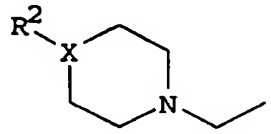


III

wherein X is N or CH; R^1 is hydrogen or methyl; and R^2 is phenyl or substituted phenyl wherein each substituent is independently selected from C_1-C_6 alkyl or sulphonamido, and the

pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

In a preferred embodiment of Formula III, the group,



is attached to the benzoxazinone group at the 6 or 7 position.

In another preferred embodiment, R^1 is hydrogen.

In another preferred embodiment, R^2 is phenyl, methyltolyl, tolyl, or sulfonamido.

In a most preferred embodiment, the compounds of Formula I, II, and III are:

4-[4-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethyl)-piperazin-1-yl]-benzenesulfonamide;

6-[4-(3,4-dimethyl-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

6-(4-p-tolyl-piperazin-1-ylmethyl)-4H-benzo[1,4]oxazin-3-one;

6-[4-phenyl-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

7-(4-p-tolyl-piperazin-1-ylmethyl)-4H-benzo[1,4]oxazin-3-one;

7-(4-phenyl-piperazin-1-ylmethyl)-4H-benzo[1,4]oxazine-3-one;

7-[4-(3,4-dimethyl-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazine-3-one;

6-[4-(5-methyl-pyridin-2-yl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

6-(4-p-tolyl-piperidin-1-ylmethyl)-4H-benxo[1,4]oxazin-3-one;

6-[4-(3,4-Dimethyl-phenyl)-piperidin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

6-(4-thiazol-2-yl-piperazin-1-ylmethyl)-4H-benzo[1,4]oxazin-3-one;

6-(4-benzothiazol-2-yl-piperazin-1-ylmethyl)-4H-benzo[1,4]oxazin-3-one;

6-[4-(4,5-dimethyl-thiazol-2-yl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

6-(4-naphthalen-2-yl-piperazin-1-ylmethyl)-4H-benzo[1,4]oxazin-3-one;

6-[4-(3-chloro-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

6-[4-(3,4-dichloro-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

2-[4-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethyl)-piperazin-1-yl]-benzonitrile;

6-[4-(4-methoxy-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

6-[4-(2-chloro-4-methyl-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

6-[4-(4-Fluoro-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

6-[4-(3-Trifluoromethyl-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

6-[4-(3,5-Dimethyl-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

6-[4-(2-Chloro-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

6-[4-(4-Trifluoromethyl-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

6-[4-(4-Chloro-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

7-[4-(5-Methyl-pyridin-2-yl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

7-[4-(4-Methoxy-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

7-[4-(4-Chloro-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

7-[4-(3,4-Dimethyl-phenyl)-piperidin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

6-[4-(4-Methoxy-phenyl)-piperidin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

7-[4-(4-Methoxy-phenyl)-piperidin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

7-(4-Phenyl-piperidin-1-ylmethyl)-4H-benzo[1,4]oxazin-3-one;

7-(4-Naphthalen-2-yl-piperazin-1-ylmethyl)-4H-benzo[1,4]oxazin-3-one; or

7-(4-p-Tolyl-piperidin-1-ylmethyl)-4H-benzo[1,4]oxazin-3-one.

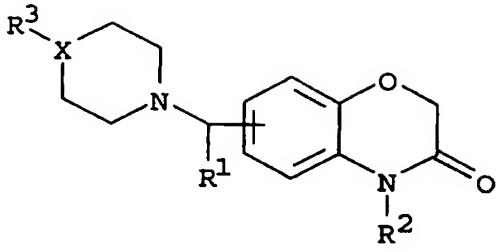
Also provided by the present invention is a method of treating psychosis, the method comprising administering to a patient suffering therefrom a therapeutically effective amount of a compound of Formula I, II, or III.

Also provided by the present invention is a method of treating schizophrenia, the method comprising administering to a patient suffering therefrom a therapeutically effective amount of a compound of Formula I, II, or III.

Also provided by the present invention is a pharmaceutically acceptable composition that comprises a compound of Formula I, II, or III.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds of the Formulas I and II



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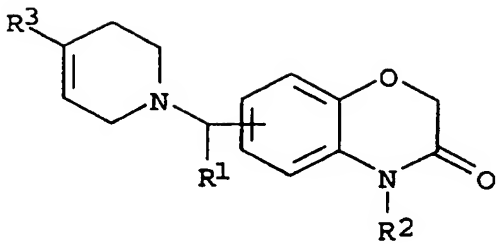


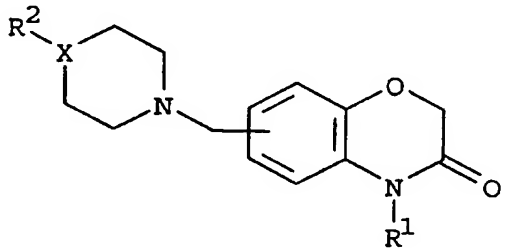
II

wherein R^1 and R^2 are independently hydrogen or C_1-C_6 alkyl;

X is N or CH; and

R^3 is phenyl, naphthyl, heteroaryl, or substituted phenyl, substituted naphthyl or substituted heteroaryl wherein each substituent is independently selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl-CN, $-CF_3$, or sulphonamido, and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof. The term substituted phenyl included phenyl substituted with one or more substituent.

The present invention also provides compounds of Formula III,



III

wherein X is N or CH; R^1 is hydrogen or methyl; and R^2 is phenyl or substituted phenyl, wherein each substituent is independently selected from C_1-C_6 alkyl or sulphonamido, and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

The term "alkyl" means a straight or branched chain hydrocarbon. Representative examples of alkyl

groups are methyl, ethyl, propyl, isopropyl, isobutyl, butyl, tert-butyl, sec-butyl, pentyl, and hexyl.

The term "aryl" means a cyclic aromatic hydrocarbon. Representative examples of aryl groups include phenyl and naphthyl, which can be substituted or unsubstituted. Examples of suitable substituents include halogen, C_1-C_6 alkyl, hydroxy, C_1-C_6 alkoxy, $-CF_3$, and sulfonamides.

The term "heteroaryl" means a cyclic hydrocarbon that contains one or more heteroatom. Representative examples of heteroaryl groups are thiazole, thiophene, and pyridine, pyrimidine, quinoline, isoquinoline, and imidazole. The heteroaryl group can be substituted or unsubstituted. Examples of suitable substituents include C_1-C_6 alkyl, C_1-C_6 alkoxy, or halogen.

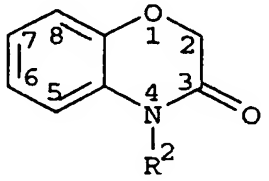
The term "heteroatom" means an atom other than carbon. Examples of heteroatoms include nitrogen, oxygen, sulfur, and phosphorus.

The term "halogen" means chlorine, fluorine, bromine, and iodine.

The term "sulfonamido" means a group having the structure $-SO_2NR^aR^b$, where R^a and R^b are sulfonamido substituents well known to those in the art such as hydrogen and C_1-C_6 alkyl.

The symbol "-" means a bond.

The atoms in the benzoxazinone group can be numbered as shown below:



The term "patient" includes humans.

A "therapeutically effective amount" is an amount of a compound of the present invention that when administered to a patient ameliorates a symptom of psychosis or schizophrenia. A therapeutically effective amount of a compound of the present invention can be easily determined by one skilled in the art by administering a quantity of a compound to a patient and observing the result. In addition, those skilled in the art are familiar with identifying patients having psychosis and schizophrenia and are readily able to identify patients who suffer from psychosis and schizophrenia.

The term "pharmaceutically acceptable salts, esters, amides, and prodrugs" as used herein refers to those carboxylate salts, amino acid addition salts, esters, amides, and prodrugs of the compounds of the present invention which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of patients without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "salts" refers to the relatively nontoxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate mesylate, glucoheptonate,

lactobionate and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. (See, for example, Berge S.M., et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977;66:1-19 which is incorporated herein by reference).

Examples of pharmaceutically acceptable, nontoxic esters of the compounds of this invention include C_1-C_6 alkyl esters wherein the alkyl group is a straight or branched chain. Acceptable esters also include C_5-C_7 cycloalkyl esters as well as arylalkyl esters such as, but not limited to benzyl. C_1-C_4 alkyl esters are preferred. Esters of the compounds of the present invention may be prepared according to conventional methods.

Examples of pharmaceutically acceptable, nontoxic amides of the compounds of this invention include amides derived from ammonia, primary C_1-C_6 alkyl amines and secondary C_1-C_6 dialkyl amines wherein the alkyl groups are straight or branched chain. In the case of secondary amines the amine may also be in the form of a 5- or 6-membered heterocycle containing one nitrogen atom. Amides derived from ammonia, C_1-C_3 alkyl primary amines and C_1-C_2 dialkyl secondary amines are preferred. Amides of the compounds of the invention may be prepared according to conventional methods.

The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formulae, for example, by

hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

The compounds of the present invention can be administered to a patient alone or as part of a composition that contains other components such as excipients, diluents, and carriers, all of which are well-known in the art. The compositions can be administered to humans and animals either orally, rectally, parenterally (intravenously, intramuscularly or subcutaneously), intracisternally, intravaginally, intraperitoneally, intravesically, locally (powders, ointments or drops), or as a buccal or nasal spray.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol,

sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid; (b) binders, as for example, carboxymethylcellulose, alignates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (c) humectants, as for example, glycerol; (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (e) solution retarders, as for example paraffin; (f) absorption accelerators, as for example, quaternary ammonium compounds; (g) wetting agents, as for example, cetyl alcohol and glycerol monostearate; (h) adsorbents, as for example, kaolin and bentonite; and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft- and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethyleneglycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with

coatings and shells, such as enteric coatings and others well-known in the art. They may contain opacifying agents and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used are polymeric substances and waxes. The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal administrations are preferably suppositories which can be prepared by mixing the compounds of the present invention with suitable nonirritating excipients or carriers such as cocoa butter, polyethyleneglycol, or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt in the rectum or vaginal cavity and release the active component.

Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

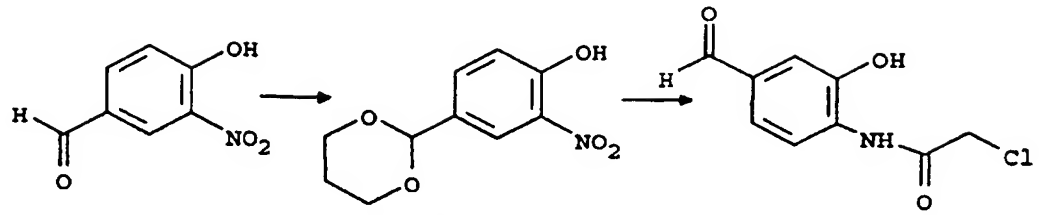
The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70 kg, a dosage in the range of about 0.01 to about 100 mg/kg of body weight per day is preferable. The specific dosage used, however, can vary. For example, the dosage can depended on a numbers of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well-known to those skilled in the art.

In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

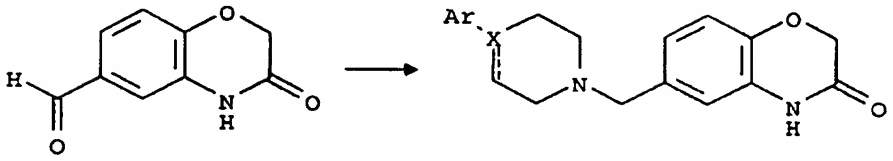
The compounds of the present invention can exist in different stereoisometric forms by virtue of the presence of asymmetric centers in the compounds. It is contemplated that all stereoisometric forms of the compounds as well as mixtures thereof, including racemic mixtures, form part of this invention.

The examples shown below illustrate particular embodiments of the invention and are not intended to limit the specification, including the claims, in any manner.

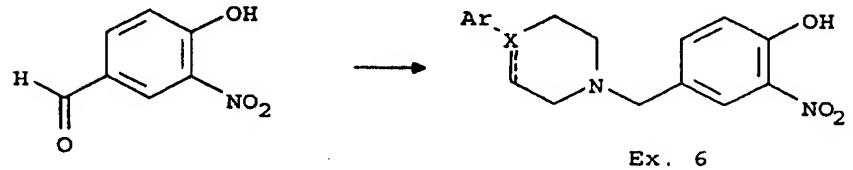
General Synthetic Schemes



Ex. 1 Ex. 2



Ex. 3 Ex. 4 and 5



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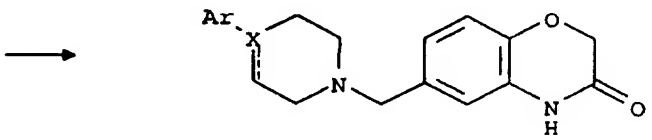
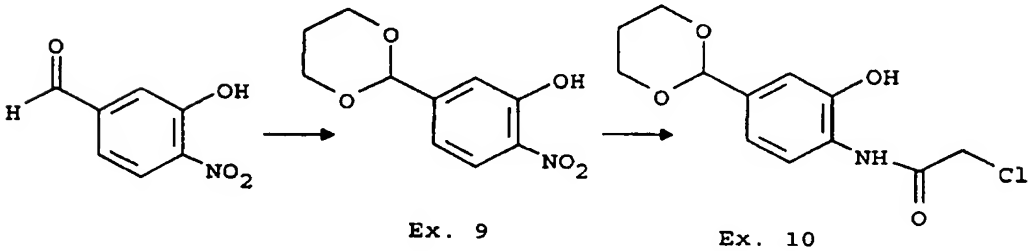
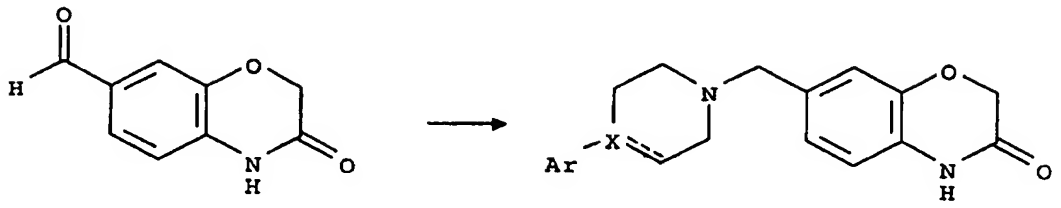


Ex. 7 and 8

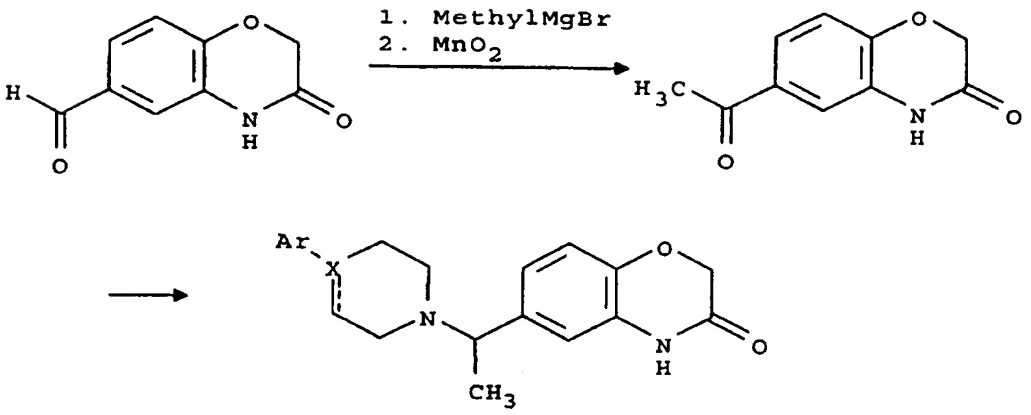


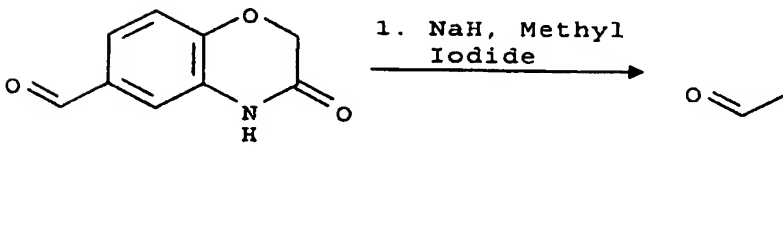
Ex. 9 Ex. 10

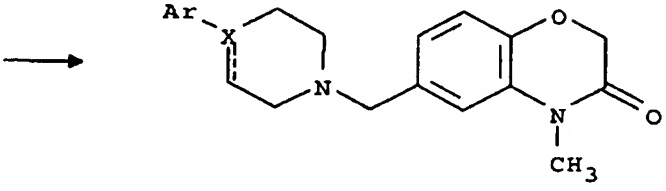
General Synthetic Schemes (continued)



Ex. 11 Ex. 12-14







EXAMPLE 1

Preparation of 2-[4-hydroxy-3-nitro-phenyl]-1,3-dioxane

A mixture of 4-hydroxy-3-nitro-benzaldehyde (5.0 g, 29.9 mmol), 1,3-propanediol (3.4 g, 44.9 mmol) and 0.1 g of p-toluene sulfonic acid in 100 mL of toluene is warmed to reflux. The water generated is removed by a Dean-Stark trap. After 2 hours, the reaction mixture is cooled to room temperature and extracted with 2 x 100 mL of saturated sodium bicarbonate followed by 100 mL of brine. Drying over sodium sulfate and evaporation of the solvent gives 5.6 g (83% yield) of 2-[4-hydroxy-3-nitro-phenyl]-1,3-dioxane oil.

NMR, $CDCl_3$: δ 1.2(d,1H), 1.5(s,1H), 2.2(m,1H), 3.9(t,2H), 4.2(d,2H), 5.4(s,1H), 7.05(d,1H), 7.6(d,1H), 8.2(s,1H).

EXAMPLE 2

Preparation of 3-(chloroacetylamino)-4-hydroxy-benzaldehyde

2-[4-Hydroxy-3-nitro-phenyl]-1,3-dioxane (5.6 g, 24.9 mmol) is reduced in the presence of Raney nickel in 50 mL of tetrahydrofuran (THF) under a hydrogen atmosphere. When the theoretical amount of hydrogen is taken up, the catalyst is removed by filtration. Chloroacetyl chloride (2.5 g, 22.2 mmol) and sodium bicarbonate (3.6 g, 42.3 mmol) are added to the filtrate at room temperature and the mixture is stirred for 1 hour under argon. The solvent is evaporated and the remaining solid is taken up in 50 mL of methanol. The solution is acidified to a pH of about one with 1.0N HCl and stirred at room temperature for 1 hour. The precipitate is collected and dried under vacuum to give 2.5 g (65% yield) of 3-(chloroacetylamino)-4-hydroxy-benzaldehyde as a hydrate; mp 190-192°C.

Analysis for $C_9H_8ClNO_3 \cdot 0.9\ H_2O$:
C, 50.41; H, 4.18; N, 6.53.
Found: C, 50.60; H, 3.83; N, 6.41.

EXAMPLE 3

Preparation of 3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbaldehyde

3-(Chloroacetylamino)-4-hydroxy-benzaldehyde (2.4 g, 13.2 mmol) and potassium carbonate (9.1 g, 66.1 mmol) are stirred at room temperature in 50 mL of acetonitrile for 12 hours. The acetonitrile is evaporated and the residue is taken up in 50 mL of water. After standing at room temperature for 10 minutes, the precipitate is collected by filtration and recrystallized from ethyl acetate to give 1.4 g (60% yield) of 3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbaldehyde; mp 220-222°C.
Analysis for $C_9H_7NO_3$:
C, 61.02; H, 3.98; N, 7.91.
Found: C, 60.67; H, 4.03; N, 7.74.

EXAMPLE 4

Preparation of 4-[4-(3-oxo-3,4-dihydro-2H-benzo[1,4]-oxazin-6-ylmethyl)-piperazin-1-yl]-benzenesulfonamide

Sodium triacetoxyborohydride (1.2 g, 5.9 mmol) is added to a solution of 3-oxo-3,4-dihydro-2H-benzo[1,4]-oxazine-6-carbaldehyde (0.5 g, 2.8 mmol) and 4-(piperazin-1-yl)-benzenesulfonamide (0.17 g, 3.1 mmol) in 20 mL of THF. The mixture is stirred at room temperature overnight. The reaction is quenched by addition of 50 mL of water, and the THF is removed under reduced pressure. The precipitate is collected by filtration and recrystallized from methanol to give 0.05 g (4% yield) of 4-[4-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethyl)-piperazin-1-yl]-benzenesulfonamide; mp 150-153°C.

Analysis for $C_{19}H_{22}N_4O_4S$:

C, 56.70; H, 5.51; N, 13.92; S, 7.97.

Found: C, 56.57; H, 5.56, N, 13.67; S, 7.80.

EXAMPLE 5

Preparation of 6-[4-(3,4-Dimethyl-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one

1-(3,4-Dimethylphenyl)-piperazine is converted to 6-[4-(3,4-dimethyl-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one in 10% yield according to the procedure of Example 4; mp 148-153°C.

Analysis for $C_{21}H_{25}N_3O_2$:

C, 71.77; H, 7.17; N, 11.96.

Found: C, 71.50; H, 7.18; N, 11.92.

EXAMPLE 6

Preparation of 4-[4-(methylphenyl)-piperazin-1-ylmethyl]-2-nitro-phenol

Sodium triacetoxyborohydride (1.8 g, 8.4 mmol) is added to a solution of 4-hydroxy-3-nitro-benzaldehyde (1.3 g, 8.0 mmol) and 1-(4-methyl-phenyl)-piperazine (2.8 g, 16.1 mmol) in 50 mL of THF at room temperature, and the mixture is stirred overnight. The reaction is quenched by pouring into 400 mL of water, and the precipitate which forms is collected by filtration. Yield = 1.7 g (33%) of 4-[4-(methylphenyl)-piperazin-1-ylmethyl]-2-nitro-phenol oil.

NMR, $CDCl_3$: δ 2.2(s,3H), 2.5(m,4H), 3.05(m,4H), 3.4(s,2H), 6.8(d,2H), 7.0(d,2H), 7.05(d,1H), 7.55(d,1H), 8.0(s,1H).

EXAMPLE 7

Preparation of 6-(4-p-tolyl-piperazin-1-ylmethyl)-4H-benzo[1,4]oxazin-3-one

4-[4-(Methylphenyl)-piperazin-1-ylmethyl]-2-nitro-phenol (1.7 g, 5.2 mmol) is reduced with Raney nickel

in 20 mL of THF under hydrogen. When the theoretical amount of hydrogen is taken up, the catalyst is removed by filtration. The THF is evaporated, and the residue is taken up in 50 mL of chloroform. Chloroacetyl chloride (0.65 g, 5.7 mmol) and sodium bicarbonate (1.6 g, 19.1 mmol) are added, and the mixture is stirred at room temperature for one-half hour, then extracted with water (3 x 50 mL) and dried over sodium sulfate. The solvent is evaporated, and the solid remaining is treated with excess potassium carbonate in 20 mL of chloroform at reflux overnight. Extraction with water, drying over sodium sulfate, and evaporation of the solvent gives a yellow solid. Recrystallization from ethyl acetate gives 0.27 g (16% yield) of 6-(4-p-tolyl-piperazin-1-ylmethyl)-4H-benzo[1,4]oxazin-3-one; mp 209-212°C.

Analysis for $C_{20}H_{23}N_3O_2$:

Calculated C, 71.19; H, 6.87; N, 12.45.

Found: C, 71.05; H, 6.97; N, 12.35.

EXAMPLE 8

Preparation of 6-[4-phenyl-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one

4-(4-Phenyl-piperazine-1-ylmethyl)-2-nitro-phenol is treated according to the procedure of Example 7 to give 6-[4-phenyl-piperazin-1-ylmethyl]-4H-benzo[1,4]-oxazin-3-one; mp 207-209°C.

EXAMPLE 9

Preparation of 2-(3-hydroxy-4-nitro-phenyl)-1,3-dioxane

3-Hydroxy-4-nitro-benzaldehyde (7.5 g, 44.9 mmol) is treated with 1,3-propanediol (5.1 g, 67.3 mmol) according to the procedure of Example 1 to give 2-(3-hydroxy-4-nitro-phenyl)-1,3-dioxane (9.6 g, 95% yield) oil.

NMR, $CDCl_3$: δ 1.4(d,1H), 7.05(d,1H), 2.2(m,1H), 3.9(t,2H), 4.2(d,2H), 5.4(s,1H), 7.2(s,1H), 8.0(d,1H).

EXAMPLE 10

Preparation of 4-(chloroacetyl-amino)-3-hydroxy-benzaldehyde

2-(3-Hydroxy-4-nitro-phenyl)-1,3-dioxane (9.3 g, 41.2 mmol) is converted to 4-(chloroacetyl-amino)-3-hydroxy-benzaldehyde according to the procedure of Example 2. Yield = 3.7 g (35%) oil.
NMR, DMSO: δ 4.4(s,1H), 7.3(s,1H), 7.4(d,1H), 8.2(d,1H), 9.7(s,1H), 9.8(s,1H), 10.7(s,1H).

EXAMPLE 11

Preparation of 3-oxo-dihydro-2H-benzo[1,4]oxazine-7-carbaldehyde

4-(Chloroacetyl-amino)-3-hydroxy-benzaldehyde (3.7 g, 17.3 mmol) is converted to 3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-7-carbaldehyde (3.2 g, 100% yield) according to the procedure of Example 3;
mp 178-180°C (Decomposes).

EXAMPLE 12

Preparation of 7-(4-p-Tolyl-piperazin-1-ylmethyl)-4H-benzo[1,4]oxazin-3-one

A mixture of 3-oxo-dihydro-2H-benzo[1,4]oxazine-7-carbaldehyde (0.5 g, 2.8 mmol), 1-(4-methyl-phenyl)-piperazine (0.5 g, 2.8 mmol), acetic acid (0.17 g, 2.8 mmol) and sodium triacetoxyborohydride (1.2 g, 5.9 mmol) in 20 mL of 1,2-dichloroethane is stirred at room temperature for 3 hours. The reaction is quenched with 50 mL of water, and the layers are separated. The aqueous phase is extracted with ethyl acetate (3 × 50 mL). The organic phases are combined and dried over sodium sulfate. Evaporation of the solvent gives a solid which is recrystallized twice from acetonitrile

to give 0.31 g (33% yield) of 7-[4-(4-methyl-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazine-3-one; mp 208-210°C.

Analysis for $C_{20}H_{23}N_3O_2$:

C, 71.19; H, 6.87; N, 12.45.

Found: C, 71.10; H, 6.73; N, 12.32.

EXAMPLE 13

Preparation of 7-(4-phenyl-piperazin-1-ylmethyl)-4H-benzo[1,4]oxazine-3-one

1-Phenyl-piperazine (0.45, 2.8 mmol) is converted to 7-(4-phenyl-piperazin-1-ylmethyl)-4H-benzo[1,4]-oxazine-3-one according to the procedure of Example 12 in 34% yield; mp 191-193°C.

EXAMPLE 14

Preparation of 7-[4-(3,4-dimethyl-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazine-3-one

According to the procedure of Example 12, 1-(3,4-dimethyl-phenyl)-piperazine (0.54 g, 2.8 mmol) is converted to 7-[4-(3,4-dimethyl-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazine-3-one in 28% yield; mp 195-197°C.

The compounds listed below can be prepared in accordance with the above methods using the appropriate starting materials.

EXAMPLES 15 - 26

Example Number	Compound Name	Elemental Analysis	Melting Point °C
15	6-[4-(5-Methyl-pyridin-2-yl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one	$C_{19}H_{22}N_4O_2$ Calculated: C, 67.44; H, 6.55; N, 16.56 Found: C, 67.35; H, 6.53; N, 16.58	207-208
16	6-(4-p-Tolyl-piperidin-1-ylmethyl)-4H-benxo[1,4]oxazin-3-one	$C_{21}H_{24}N_2O_2$ Calculated: C, 74.96; H, 7.20; N, 8.33 Found: C, 74.73; H, 7.30; N, 8.36	178-180
17	6-[4-(3,4-Dimethyl-phenyl)-piperidin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one	$C_{22}H_{26}N_2O_2$ Calculated: C, 75.40; H, 7.48; N, 7.99 Found: C, 75.39; H, 7.62; N, 8.10	165-169

Example Number	Compound Name	Elemental Analysis	Melting Point °C
18	6-(4-thiazol-2-yl-piperazin-1-ylmethyl)-4H-benzo[1,4]oxazin-3-one	$C_{16}H_{18}N_4O_2S$ Calculated: C, 58.16; H, 5.49; N, 16.96 Found: C, 58.32; H, 5.59; N, 17.03	210-212
19	6-(4-Benzothiazol-2-yl-piperazin-1-ylmethyl)-4H-benzo[1,4]oxazin-3-one	$C_{20}H_{20}N_4O_2S$ Calculated: C, 63.14; H, 5.30; N, 14.73 Found: C, 62.72; H, 5.24; N, 14.45	240-243
20	6-[4-(4,5-dimethyl-thiazol-2-yl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one	$C_{18}H_{22}N_4O_2S$ Calculated: C, 60.31; H, 6.19; N, 15.63; S, 8.94 Found: C, 60.31; H, 6.11; N, 15.56; S, 9.21	210-212
21	6-(4-Naphthalen-2-yl-piperazin-1-ylmethyl)-4H-benzo[1,4]oxazin-3-one	$C_{23}H_{23}N_3O_2$ Calculated: C, 73.97; H, 6.21; N, 11.25 Found: C, 73.70; H, 6.21; N, 10.90	215-216

Example Number	Compound Name	Elemental Analysis	Melting Point °C
22	6-[4-(3-Chloro-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one	$C_{19}H_{20}ClN_3O_2$ Calculated: C, 63.77; H, 5.63; N, 11.74 Found: C, 63.78; H, 5.50; N, 11.54	199-200
23	6-[4-(3,4-Dichloro-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one	$C_{19}H_{19}Cl_2N_3O_2$ Calculated: C, 58.17; H, 4.88; N, 10.71 Found: C, 58.30; H, 4.77; N, 10.43	174-175
24	2-[4-(3-Oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethyl)-piperazin-1-yl]-benzonitrile	$C_{20}H_{20}N_4O_2$ Calculated: C, 68.95; H, 5.79; N, 16.08 Found: C, 68.91; H, 5.78; N, 15.93	195-196
25	6-[4-(4-Methoxy-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one	$C_{20}H_{23}N_3O_3$ Calculated: C, 67.97; H, 6.56; N, 11.80 Found: C, 67.87; H, 6.56, N, 11.72	202-203

Example Number	Compound Name	Elemental Analysis	Melting Point °C
26	6-[4-(2-Chloro-4-methyl-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one	$C_{20}H_{22}ClN_3O_2$ Calculated: C, 64.60; H, 5.96; N, 11.30; Cl, 9.53 Found: C, 64.21; H, 5.79; N, 11.01; Cl, 9.47	188-189
27	6-[4-(4-Fluoro-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one	$C_{19}H_{20}FN_3O_2$ Calculated: C, 66.85; H, 5.91; N, 12.31 Found: C, 66.56; H, 5.88; N, 12.12	226-227
28	6-[4-(3-Trifluoromethyl-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one	$C_{20}H_{20}F_3N_3O_2$ Calculated: C, 61.38; H, 5.15; N, 10.74 Found: C, 61.29; H, 5.12; N, 10.64	191-192
29	6-[4-(3,5-Dimethyl-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one	$C_{21}H_{25}N_3O_2$ Calculated: C, 71.77; H, 7.17; N, 11.96 Found: C, 71.53; H, 7.03; N, 11.84	164-165

Example Number	Compound Name	Elemental Analysis	Melting Point °C
30	6-[4-(2-Chloro-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one	$C_{19}H_{20}ClN_3O_2$ Calculated: C, 63.77; H, 5.63; N, 11.74 Found: C, 63.45; H, 5.59; N, 11.67	188-189
31	6-[4-(4-Trifluoromethyl-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one	$C_{20}H_{20}F_3N_3O_2$ Calculated: C, 61.38; H, 5.15; N, 10.74 Found: C, 61.31; H, 5.31, N, 10.64	220
32	6-[4-(4-Chloro-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one	$C_{19}H_{20}ClN_3O_2 \cdot 0.5H_2O$ Calculated: C, 62.20; H, 5.77; N, 11.46 Found: C, 62.50; H, 5.81; N, 11.29	250-251.5
33	7-[4-(5-Methyl-pyridin-2-yl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one	$C_{19}H_{22}N_4O_2$ Calculated: C, 67.44; H, 6.55; N, 16.56 Found: C, 67.35; H, 6.60; N, 16.40	215

Example Number	Compound Name	Elemental Analysis	Melting Point °C
34	7-[4-(4-Methoxy-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one	$C_{20}H_{23}N_3O_3$ Calculated: C, 67.97; H, 6.56; N, 11.89 Found: C, 67.72; H, 6.46; N, 11.7	235
35	7-[4-(4-Chloro-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one	$C_{19}H_{20}ClN_3O_2$ Calculated: C, 63.77; H, 5.63; N, 11.74 Found: C, 62.55; H, 5.54; N, 11.42	232-233
36	7-[4-(3,4-Dimethyl-phenyl)-piperidin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one	$C_{22}H_{26}N_2O_2$ Calculated: C, 75.40; H, 7.48; N, 7.99 Found: C, 75.17; H, 7.25; N, 7.84	192-194
37	6-[4-(4-Methoxy-phenyl)-piperidin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one	$C_{21}H_{24}N_2O_3$ Calculated: C, 71.50; H, 6.86; N, 7.95 Found: C, 71.14; H, 6.62; N, 7.60	177-178

Example Number	Compound Name	Elemental Analysis	Melting Point °C
38	7-[4-(4-Methoxy-phenyl)-piperidin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one	$C_{21}H_{24}N_2O_3$ Calculated: C, 71.57; H, 6.86; N, 7.95 Found: C, 71.29; H, 6.83; N, 7.75	198-199
39	7-(4-Phenyl-piperidin-1-ylmethyl)-4H-benzo[1,4]oxazin-3-one	$C_{20}H_{22}N_2O_2$ Calculated: C, 74.51; H, 6.88; N, 8.62 Found: C, 74.59; H, 6.74; N, 8.69	184-186
40	7-(4-Naphthalen-2-yl-piperazin-1-ylmethyl)-4H-benzo[1,4]oxazin-3-one	$C_{23}H_{23}N_3O_2$ Calculated: C, 73.97; H, 6.21; N, 11.25 Found: C, 73.62; H, 6.07; N, 11.40	247-249
41	7-(4-p-Tolyl-piperidin-1-ylmethyl)-4H-benzo[1,4]oxazin-3-one	$C_{21}H_{24}N_2O_2$ Calculated: C, 74.97; H, 7.19; N, 8.33 Found: C, 74.61; H, 7.00; N, 8.55	186-188

BIOLOGICAL METHODS

Cell Lines Expressing Dopamine Receptor Isoforms

A cell line expressing human dopamine D2 (Long form) receptors was purchased from Oregon Health Sciences University, Portland, Oregon. The D2 receptor cDNA was subcloned into an expression vector, pRc/CMV. The plasmids were transfected by electroporation into CHO K1 cells. A single stable transfectant, resistant to the antibiotic G418, was isolated and selected for use in the binding studies. For D4 binding, CHO K1 cells stably transfected to express the human recombinant dopamine D4.2 receptor subtype, as described by Shih, et al., "The expression and functional characterization of human dopamine D4.2 receptor in CHO K1 cells," Soc. Neurosci., 1995;21(Part 1):621.

Cell Culture and Preparation of Cell Membranes

CHO K1 cells expressing either human D2 and D4.2 receptors were grown in 162 cm^2 culture flasks in F12 medium (Gibco Laboratories, Grand Island, New York) supplemented with 10% fetal bovine serum (FBS, Hyclone, Logan, UT) in an atmosphere of 5% CO_2/95% air at 37°C. Cells were grown until confluent, after which growth medium was removed and replaced with 0.02% ethylene diamine tetracetate (EDTA) in a phosphate-buffered saline solution (Sigma Chemical Co., St. Louis, Missouri) and scraped from the flasks. The cells were centrifuged at about 1000 x g for 10 minutes at 40°C and then resuspended in TEM buffer (25 mM Tris-HCl, pH 7.4, 5 mM EDTA, and 6 mM $MgCl_2$) for D2 or the D4.2 buffer (50 mM Tris-HCl, pH 7.4, 5 mM EDTA, 1.5 mM $CaCl_2$, 5 mM KCl, and 120 mM NaCl) and homogenized. The membranes were pelleted by centrifugation at 20,000 x g at 40°C for 20 minutes. Then the pellets were resuspended in appropriate buffer at 1 mL/flask and

stored at -70°C until used in the receptor binding assay.

Receptor Binding Assays: D2, D4.2 Dopamine Receptors

A cell membrane preparation (400 μL) was incubated in triplicate with 50 μL [^{3}H]spiperone (0.2 nM for D2, 0.2 nM for D4.2), 50 μL buffer, or competing drugs where appropriate to give a final volume of 0.5 mL. After 60 minutes incubation at 25°C, the incubations were terminated by rapid filtration through Whatmann GF/B glass fibre filters (soaked for 1 hour in 0.5% polyethylenimine) on a -cell harvester, with three washes of 1 mL ice-cold buffer. Individual filter disks containing the bound ligand were placed in counting vials with 4 mL of scintillation fluid (Ready Gel, Beckman Instrument Inc., Fullerton, California) and then counted in a Beckman LS-6800 liquid scintillation counter at an efficiency of 45%. Nonspecific binding was defined in presence of 1 mM of haloperidol.

Data Calculation

Saturation and competition binding data were analyzed using an iterative nonlinear least-square curve-fitting Ligand program. In competition experiments, apparent K_i values were calculated from IC_{50} values by method of Cheng and Prusoff, "Relationship between the inhibition constant (K_i) and the concentration of inhibitor which causes 50% inhibition (IC_{50}) of an enzymatic reaction," Biochem. Pharmacol., 1973;22:3099-3108. Experimental compounds were made up as stock solutions in dimethyl sulfoxide (DMSO). The final concentration of 0.1% DMSO used in the incubation mixture had no effect on the specific binding. Each observation was carried out in triplicate. To allow these calculations, K_i values were measured for the interaction of various ligands with the receptor. These were: [^{3}H]spiperone binding,

human D2, 0.116 + 0.01 and human D4.2, 0.093 + 0.005 nM (n = 3). The test results are presented below.

BINDING DATA

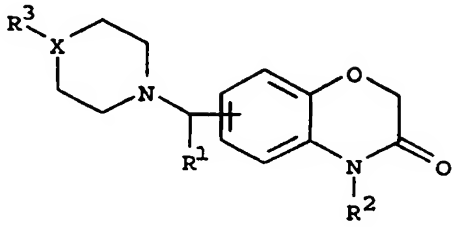
Example Number	D2 (Ki, nM)	D4 (Ki, nM)	D2/D4 Ratio
1	493	4.36	113.1
3		1665	
4	>5882	23.56	249.7
5	2341	5.18	451.9
8	2196	18.3	120
12	2983	10.66	279.8
13	129	6.09	21.2
14	346	6.94	49.9
15	>5882	7.17	820.4
16	52.50	2.84	18.5
17	572	1.81	316
18		125.88	
19		33.30	
20	>5882	10.77	546.1
21	4325	17.83	242.6
22	3887	15.41	252.2
23	2616	19.01	137.6
24	435	6.06	71.8
25	5592	12.34	453.2
26	127	8.84	14.4
27	2616	15.61	167.6
28	3582	15.66	228.7
29	1434	12.12	118.3
30	72	13.03	5.5
31		173	
32	>5882.4	62.47	94.2
33	1753	1.66	1056
34	5882.40	5.0	1176.5
35	620	4.68	132.5
36	610	2.61	233.7
37	698	3.87	180.4

BINDING DATA (cont'd)

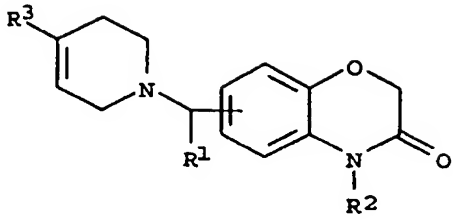
Example Number	D2 (Ki, nM)	D4 (Ki, nM)	D2/D4 Ratio
38	1126	6.70	168.1
39	68.98	7.58	9.1
40	673.92	13.85	48.7
41	287.31	2.60	110.5

CLAIMS

1. A compound having the Formula I or II



I



II

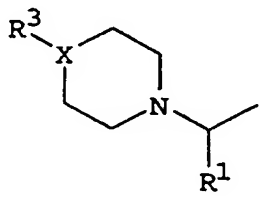
wherein R^1 and R^2 are independently hydrogen or C_1-C_6 alkyl;

X is N or CH; and

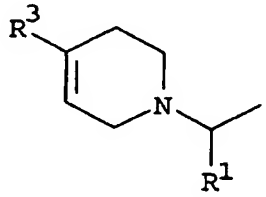
R^3 is phenyl, naphthyl, heteroaryl, substituted phenyl, substituted naphthyl or substituted heteroaryl

wherein each substituent is independently selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, -CN, -CF_3, or sulphonamido, and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

2. A compound of Claim 1 wherein the group



or



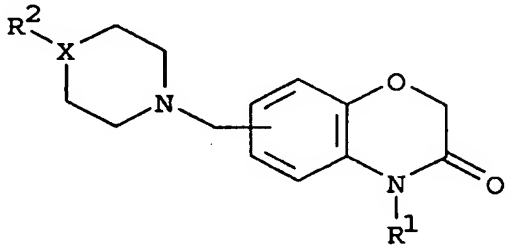
is attached to the benzoxazinone group at the 6 or 7 position.

3. A compound of Claim 1 wherein R^1 and R^2 are hydrogen.

4. A compound of Claim 1 wherein R^3 is phenyl, methyltolyl, tolyl or sulfonamido.

5. A compound of Claim 1 wherein X is N.

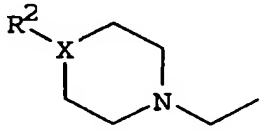
6. A compound having the Formula III,



III

wherein X is N or CH; R^1 is hydrogen or methyl; and
R^2 is phenyl or substituted phenyl wherein each substituent is independently selected from C_1-C_6 alkyl or sulphonamido, and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

7. A compound of Claim 6 wherein the group,



is attached to the benzoxazinone group at the 6 or 7 position.

8. A compound of Claim 6 wherein R^1 and R^2 are hydrogen.

9. A compound of Claim 6 wherein R^2 is phenyl, methyltolyl, tolyl, or sulfonamido.

10. A compound of Claim 1 wherein the compound is
4-[4-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethyl)-piperazin-1-yl]-benzenesulfonamide;
6-[4-(3,4-dimethyl-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;
6-(4-p-tolyl-piperazin-1-ylmethyl)-4H-benzo[1,4]oxazin-3-one;
6-[4-phenyl-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;
7-(4-p-tolyl-piperazin-1-ylmethyl)-4H-benzo[1,4]oxazin-3-one;
7-(4-phenyl-piperazin-1-ylmethyl)-4H-benzo[1,4]oxazine-3-one;
7-[4-(3,4-dimethyl-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazine-3-one;
6-[4-(5-methyl-pyridin-2-yl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;
6-(4-p-tolyl-piperidin-1-ylmethyl)-4H-benxo[1,4]oxazin-3-one;
6-[4-(3,4-Dimethyl-phenyl)-piperidin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;
6-(4-thiazol-2-yl-piperazin-1-ylmethyl)-4H-benzo[1,4]oxazin-3-one;
6-(4-benzothiazol-2-yl-piperazin-1-ylmethyl)-4H-benzo[1,4]oxazin-3-one;
6-[4-(4,5-dimethyl-thiazol-2-yl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;
6-(4-naphthalen-2-yl-piperazin-1-ylmethyl)-4H-benzo[1,4]oxazin-3-one;
6-[4-(3-chloro-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;
6-[4-(3,4-dichloro-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

2-[4-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethyl)-piperazin-1-yl]-benzonitrile;

6-[4-(4-methoxy-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one; or

6-[4-(2-chloro-4-methyl-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one.

11. A compound of Claim 1 wherein the compound is

6-[4-(4-Fluoro-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

6-[4-(3-Trifluoromethyl-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

6-[4-(3,5-Dimethyl-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

6-[4-(2-Chloro-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

6-[4-(4-Trifluoromethyl-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

6-[4-(4-Chloro-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

7-[4-(5-Methyl-pyridin-2-yl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

7-[4-(4-Methoxy-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

7-[4-(4-Chloro-phenyl)-piperazin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

7-[4-(3,4-Dimethyl-phenyl)-piperidin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

6-[4-(4-Methoxy-phenyl)-piperidin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

7-[4-(4-Methoxy-phenyl)-piperidin-1-ylmethyl]-4H-benzo[1,4]oxazin-3-one;

7-(4-Phenyl-piperidin-1-ylmethyl)-4H-benzo[1,4]oxazin-3-one;

7-(4-Naphthalen-2-yl-piperazin-1-ylmethyl)-4H-benzo[1,4]oxazin-3-one; and

30 7-(4-p-Tolyl-piperidin-1-ylmethyl)-4H-benzo[1,4]oxazin-3-one.

12. A method of treating psychosis, the method comprising administering to a patient suffering therefrom a therapeutically effective amount of a compound of Claim 1.

13. A method of treating psychosis, the method comprising administering to a patient suffering therefrom a therapeutically effective amount of a compound of Claim 6.

14. A method of treating schizophrenia, the method comprising administering to a patient suffering therefrom a therapeutically effective amount of a compound of Claim 1.

15. A method of treating schizophrenia, the method comprising administering to a patient suffering therefrom a therapeutically effective amount of a compound of Claim 6.

16. A pharmaceutically acceptable composition that comprises a compound of Claim 1.

17. A pharmaceutically acceptable composition that comprises a compound of Claim 6.

INTERNATIONAL SEARCH REPORT

Intern ıal Application No
PCT/US 97/08524

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D265/36 C07D413/12 C07D413/06 C07D417/12 A61K31/535

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 154 969 A (MITSUBISHI CHEMICAL INDUSTRIES LTD.) 18 September 1985 see claims ---	1-17
A	EP 0 233 728 A (TAKEDA CHEMICAL INDUSTRIES, LTD.) 26 August 1987 see claims ---	1-17
A	WO 94 03426 A (SMITHKLINE BEECHAM PLC) 17 February 1994 see claims -----	1-17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
12 August 1997	15. 09. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Chouly, J

INTERNATIONAL SEARCH REPORT

In. ational application No.
PCT/US 97/08524

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 12-15
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. ..al Application No
PCT/US 97/08524

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		JP 1834889 C	11-04-94
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